EXHIBIT F

Reply Under 37 C.F.R. § 1.116
Expedited Procedure
Art Unit: 1646

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(PATENT)

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Applicants: Alitalo et al.

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For: Flt4 (VEGFR-3) as a Target for Tumor Imaging and Anti-Tumor Therapy

Examiner: Joseph F. Murphy

Group Art Unit: 1646

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AMENDMENT IN RESPONSE TO FINAL OFFICE ACTION

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Sir:

This paper is filed in response to an Office Action mailed by the U.S. Patent and Trademark Office on April 8, 2003 (hereinafter, the "Office Action"). This response is due on August 8, 2003, by virtue of the petition and fee for a one-month extension of time filed herewith. No additional fees are believed to be due; however, should any fees be necessary in connection with this document, or should the extension of time fee be inadvertently omitted, the Commissioner is hereby authorized to deduct any such fees from Marshall, Gerstein & Borun, LLP account number 13-2855.

Amendments to the Specification. There are **no** amendments to the specification.

Amendments to the claims are reflected in the complete listing of claims pursuant to 37 C.F.R. §1.121, which begins on page **2** of this paper.

Remarks begin on page **9** of this paper.

AMENDMENTS

In the Claims:

Pursuant to 37 C.F.R. §1.121 the following is a complete listing of the claims of the present application:

1. (previously presented) A method of inhibiting Flt4 receptor tyrosine kinase (Flt4) function in a mammalian organism, comprising the step of administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said organism, thereby inhibiting Flt4 function, wherein said inhibitor comprises a polypeptide selected from the group consisting of:

(a) a polypeptide comprising an antigen binding fragment of an anti Flt4 antibody; and

(b) a polypeptide comprising a soluble Flt4 fragment, wherein said fragment and said polypeptide are capable of binding to an Flt4 ligand.

2. (original) A method according to claim 1 wherein said cells comprise endothelial cells.

3. (original) A method according to claim 2 wherein said organism is human.

4. (canceled)

5. (previously presented) A method according to claim 7 wherein said inhibitor further comprises an anti-neoplastic agent conjugated to said antibody or antibody fragment.

6. (previously presented) A method according to claim 3 wherein said composition further comprises a pharmaceutically acceptable diluent, adjuvant, or carrier medium.

7. (previously presented) A method according to claim 3 wherein said inhibitor comprises an anti Flt4 antibody or fragment thereof that binds to Flt4.

8. (previously presented) A method according to claim 3 wherein said organism has a neoplastic disease characterized by expression of Flt4 tyrosine kinase (Flt4) in vascular endothelial cells,

wherein said composition comprises an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in vascular endothelial cells of said organism, and

wherein said composition is administered in an amount effective to inhibit Flt4-mediated proliferation of said vascular endothelial cells, thereby inhibiting Flt4-mediated proliferation of said vascular endothelial cells.

9. (original) A method according to claim 8 wherein said neoplastic disease is selected from the group consisting of carcinomas, squamous cell carcinomas, lymphomas, melanomas, and sarcomas.

10. (canceled)

11. (previously presented) A method according to claim 10 wherein said inhibitor comprises a polypeptide comprising an antigen-binding fragment of an anti-Flt4 antibody.

12. - 42. (canceled)

43. (previously presented) A method for antagonizing the function of Flt4 receptor tyrosine kinase (Flt4) in an organism that expresses Flt4, comprising a step of administering to the organism a composition comprising a Flt4 antibody or Flt4 binding fragment thereof in a pharmaceutically acceptable carrier.

44. (previously presented) A method according to claim 43, wherein the organism is human.

45. (previously presented) A method according to claim 44 wherein said composition further comprises an anti-neoplastic agent conjugated to said antibody or antibody fragment.

46. (previously presented) A method according to claim 44, wherein the organism has a neoplastic disorder characterized by lymphatic vessels comprising lymphatic endothelia that express Flt4.

47. (canceled)

48. (previously presented) A method for antagonizing the function of Flt4 receptor tyrosine kinase (Flt4) in an organism that expresses Flt4, comprising a step of administering to the organism a composition comprising a soluble fragment of Flt4 in a pharmaceutically acceptable carrier, wherein the fragment binds to a Flt4 ligand.

49. (previously presented) A method according to claim 48, wherein the organism is human.

50. (previously presented) A method according to claim 49, wherein the organism has a neoplastic disorder characterized by lymphatic vessels comprising lymphatic endothelia that express Flt4.

51. (canceled)

52. (previously presented) A method of inhibiting neoplastic cell growth in a mammalian subject, comprising steps of:

(a) screening a mammalian subject to identify a neoplastic disorder characterized by cells expressing Flt4 receptor tyrosine kinase (Flt4); and

(b) administering a composition to a mammalian subject identified according to step (a) as having a neoplastic disorder characterized by cells expressing Flt4, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said subject, thereby inhibiting Flt4-mediated proliferation of said Flt4-expressing cells, wherein said inhibitor comprises a polypeptide selected from the group consisting of:

(i) a polypeptide comprising an antigen binding fragment of an anti Flt4 antibody; and

(ii) a polypeptide comprising a soluble Flt4 fragment, wherein said fragment and said polypeptide are capable of binding to an Flt4 ligand.

53. (previously presented) A method according to claim 52, wherein the mammalian subject is human.

54. (canceled)

55. (previously presented) A method according to claim 53, wherein step (a) comprises screening for a neoplastic disorder characterized by undesirable lymphatic vessels comprising lymphatic endothelia that express Flt4.

56. (previously presented) A method according to claim 53, wherein step (a) comprises screening for a neoplastic disorder characterized by neoplastic cells that express Flt4.

57. (previously presented) A method according to claim 56, wherein the neoplastic cells comprise lymphoma cells that express Flt4.

58. (canceled)

59. (previously presented) A method according to claim 53 wherein said composition further comprises a pharmaceutically acceptable diluent, adjuvant, or carrier medium.

60. (previously presented) A method according to claim 53 wherein said inhibitor comprises an anti-Flt4 antibody or fragment thereof.

61. (previously presented) A method according to claim 53, wherein the inhibitor comprises an extracellular domain fragment of human Flt4.

62. (canceled)

63. (canceled)

64. (previously presented) A method according to claim 53, wherein the screening step comprises:

(a) contacting tissue from the human subject with a composition comprising an Flt4 binding compound; and

(b) screening for a neoplastic disorder characterized by cells expressing Flt4 by detecting said Flt4 binding compound bound to said tissue.

65. (previously presented) A method according to claim 64 wherein said Flt4 binding compound is an antibody that specifically binds Flt4 or an antigen-binding fragment thereof.

66. (previously presented) A method according to claim 65, wherein said antibody or fragment further comprises a detectable label covalently bound thereto.

67. (previously presented) A method according to claim 53, wherein the screening step comprises:

(a) administering a composition to the human subject, said composition comprising an antibody that specifically binds Flt4 or an antigen-binding fragment thereof; and

(b) screening for a neoplastic disorder characterized by cells expressing Flt4 by detecting said antibody or said fragment bound to cells in said human subject, thereby detecting Flt4 expressed on the surface of cells in said human subject.

68. (previously presented) A method according to claim 67, wherein said antibody or antibody fragment further comprises a detectable label.

69. (previously presented) A method according to claim 52, wherein the screening step comprises:

(a) contacting tissue from the mammalian subject with a composition comprising an antibody or antibody fragment that specifically binds Flt4;

(b) detecting said antibody or antibody fragment bound to cells in said tissue; and

(c) screening for a neoplastic disorder from the quantity or distribution of said antibody bound to cells in said tissue.

70. (canceled)

71. (canceled)

72. (previously presented) A method according to claim 69, wherein in said screening step, the screening comprises measuring the quantity or distribution of said antibody bound to lymphatic vessels.

73. (previously presented) A method of treating a mammal having breast cancer characterized by endothelial cells that express Flt4 tyrosine kinase (Flt4), comprising a step of administering to said mammal a composition, said composition comprising an inhibitor of binding between Flt4 ligand protein and Flt4 expressed in cells of said organism, thereby inhibiting Flt4 function, wherein the inhibitor comprises a member selected from the group consisting of:

(a) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment thereof;

(b) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment thereof;

(c) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment thereof; and

(d) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21).

74. (previously presented) A method according to claim 73, wherein the mammal is human.

75. (previously presented) A method according to claim 74, comprising a screening step preceding the administering step,

wherein the screening step comprises screening a human to identify breast cancer characterized by endothelial cells expressing Flt4; and

wherein the administering step comprises administering the composition to a human identified by the screening step as having breast cancer characterized by endothelial cells expressing Flt4.

76. (canceled)

77. (previously presented) A method according to any one of claims 74-76 wherein the inhibitor comprises a member selected from the group consisting of:

(a) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment thereof; and

(b) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21).

78. (previously presented) A method according to claim 73, wherein the inhibitor further comprises an anti-neoplastic agent conjugated to the antibody or polypeptide.

79. (previously presented) A method according to claim 73, wherein the composition further comprises a pharmaceutically acceptable diluent, adjuvant, or carrier.

80. - 88. (canceled)

89. (previously presented) A method of inhibiting proliferation of cells in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in cells, comprising the step of administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said organism, thereby inhibiting Flt4-mediated proliferation of the cells, wherein said inhibitor comprises a polypeptide selected from the group consisting of:

(a) a polypeptide comprising an antigen binding fragment of an anti Flt4 antibody; and

(b) a polypeptide comprising a soluble Flt4 fragment, wherein said fragment and said polypeptide are capable of binding to an Flt4 ligand.

90. (previously presented) A method according to claim 89 wherein said cells comprise endothelial cells.

91. (previously presented) A method according to claim 90, wherein said cells comprise lymphatic endothelial cells, and said composition inhibits lymphatic vascularization.

92. (canceled)

93. (previously presented) A method according to claim 90 wherein said organism is human.

94. (canceled)

95. (previously presented) A method according to claim 89 wherein said composition further comprises a pharmaceutically acceptable diluent, adjuvant, or carrier medium.

96. (previously presented) A method according to claim 93 wherein said inhibitor comprises an anti Flt4 antibody or fragment thereof that binds to Flt4.

97. (previously presented) A method according to claim 96 wherein said inhibitor further comprises an anti-neoplastic agent conjugated to said antibody or antibody fragment.

98. (previously presented) A method according to claim 93, wherein the inhibitor comprises an anti-Flt4 antibody.

99. (previously presented) A method according to claim 93 wherein the inhibitor comprises a polypeptide comprising an antigen-binding fragment of an anti-Flt4 antibody.

100. - 103. (canceled) .

104. (presently amended) A method according to claim ~~103~~ 93 wherein said neoplastic disease is selected from the group consisting of carcinomas, squamous cell carcinomas, lymphomas, melanomas, and sarcomas.

105. (canceled)

106. (canceled)

107. (presently amended) A method according to claim ~~106~~ 95 wherein the inhibitor comprises a polypeptide comprising an antigen-binding fragment of an anti-Flt4 antibody.

108. - 110. (canceled)

111. (previously presented) A method according to claim 93, wherein the disease is a cancer characterized by metastatic lymph nodes.

112. - 115. (canceled)

116. (previously presented) A method of inhibiting genesis of lymphatic vessels in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in lymphatic vessels, comprising the step of administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said organism, thereby inhibiting Flt4-mediated

proliferation of the cells, wherein said inhibitor comprises a member selected from the group consisting of:

(a) an anti-Flt4 antibody;

(b) a polypeptide comprising an antigen binding fragment of an anti Flt4 antibody; and

(c) a polypeptide comprising a soluble Flt4 fragment, wherein said fragment and said polypeptide are capable of binding to an Flt4 ligand.

117. (previously presented) A method according to claim 116 wherein said organism is human.

118. (canceled)

119. (previously presented) A method according to claim 117, wherein the human has a cancer characterized by lymph node metastases.

120. - 125. (canceled)

126. (previously presented) A method of treating a human having breast cancer characterized by endothelial cells that express Flt4 tyrosine kinase (Flt4), comprising a step of administering to said human a composition, said composition comprising an inhibitor of binding between Flt4 ligand protein and Flt4 expressed in cells of said human, thereby inhibiting Flt4 function,

wherein the inhibitor comprises a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

127. (previously presented) A method according to claim 126, comprising a screening step preceding the administering step,

wherein the screening step comprises screening a human to identify breast cancer characterized by endothelial cells expressing Flt4; and

wherein the administering step comprises administering the composition to a human identified by the screening step as having breast cancer characterized by endothelial cells expressing Flt4.

128. - 131. (canceled)

REMARKS

I. Explanation for Amendments

Claims 1-3, 5-14, 43-57, 59-79, 82-93, 95-112, and 123-131 are pending in the instant application. Claims 15-42, previously withdrawn from consideration by virtue of Applicant's election in response to the restriction requirement, have been canceled. Rejected claims 84-88 have been canceled solely to expedite allowance. Finally, claims 10, 12-14, 47, 51, 54, 62-63, 70-71, 76, 82-83, 87, 92, 100-103, 105-106, 108-110, 112-113, 115, 120-125, and 128-131 have been canceled solely for the purpose of pursuing the subject matter in a related application to maximize the patent term. Thus, Applicants reserve the right to pursue the nonelected and/or canceled subject matter in related applications, such as divisional applications.

II. The rejection of claims 84-88 under 35 U.S.C. §112 should be withdrawn.

Claims 84-88 were rejected under 35 U.S.C. §112, first paragraph, for alleged lack of written description in the specification. Notwithstanding Applicants disagreement with the Exmainer's assertion, claims 84-88 have been canceled in the instant amendment. Accordingly, Applicants respectfully request that the rejection be withdrawn, and the application be passed to allowance.

CONCLUSION

The Examiner indicated in the final Office Action that claims 1-3, 5-14, 43-57, 59-79, 89-93, 95-112, and 123-131 were allowable, and claims 84-88 were rejected. Accordingly, Applicants believe that the foregoing cancellation of claims 84-88 place the application in condition for allowance. However, if the Examiner has questions, or identifies any remaining issues preventing allowance that might be resolved by a telephonic interview or examiner's amendment, the Applicants request and invite the examiner to telephone the undersigned attorney to resolve such questions or issues.

Respectfully submitted,

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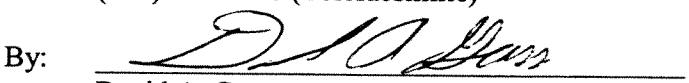
Dated: August 8, 2003 By: 

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